REMARKS

Status of Claims

Claims 80-83 and 87-93 are currently pending. Claim 80 is amended. Support for the amended and added claims is found throughout the specification as originally filed. Accordingly, Applicants submit that no new matter is introduced into the specification by way of the present amendments pursuant to 35 U.S.C. § 132. Applicants respectfully request entry of the amendments, reconsideration of the rejections, and allowance of the pending claims.

35 U.S.C. § 103(a): Yan and Milbrandt

Claims 80-83 and 87-90 and 93 are rejected under 35 U.S.C. § 103(a) as allegedly being unpatentable over Yan *et al.* (U.S. Patent No. 5,641,749; "Yan") in view of Milbrandt *et al.* (U.S. Patent No. 6,284,540; "Milbrandt"). Applicants respectfully request withdrawal of this rejection for the reasons provided herein.

The examiner maintained this rejection under the rationale that Milbrandt teaches that "NBN/ARTN can bind and activate GFRα1" and that "not only does NBN/ARTN belong to the GDNF family, it also functions as GDNF."[1/] These conclusions, however, are not factually supported by Milbrandt, nor are they supported by the general understanding in the art. Milbrandt does not teach that NBN/ARTN can bind and activate GFRα1. Nor does Milbrandt teach the *in vivo* activation of GFRα1 by NBN/ARTN. Milbrandt reports the activation of GFRα-1 in *in vitro* receptor activation experiments, in which GFRα-1 was over-expressed in neuroblastoma cells. These results, however, are not physiologically significant, but rather are an artifact of the experimental conditions (*i.e.*, the overexpression of GFRα-1). Indeed, Milbrandt

1/ Office Action at page 3, lines 18-22.

expressly states that the GFRα1-Fc fusion protein did not bind NBN/ARTN[2/] and that "direct binding of artemin to GFRα1-Fc … was not observed."[3/]

As explained in the Declaration of Teit Johansen filed herewith, Milbrandt is an author of a paper, Rakowicz, that reports GDNF is the exclusive physiological ligand for GFRα-1.[4/] A subsequent study by Carmillo[5/] confirms the findings of Rakowicz. Accordingly, the teachings of Milbrandt (US 6,284,549) have been demonstrated as incorrect, or in the least, as not physiologically relevant. Indeed, the evidence of record indicates that Milbrandt has himself admitted that GDNF is the exclusive physiological ligand for GFRα-1. Consequently, Applicants maintain that GDNF and ARTN/NBN are structurally distinct and that the skilled artisan cannot extrapolate the biological activity of GDNF to ARTN/NBN.

Further, as explained in the Declaration of Teit Johansen filed herewith, the present Specification also provides data to show that ARTN/NBN exhibits high affinity for GFRα-3, and that GDNF does not bind to GFRα-3, but rather binds to GFRα-1.[6/] Specifically, the Specification highlights the functional difference between ARTN/NBN and GDNF as follows:[7/]

> [N]eublastin binds to GFRα-3 but not to GFRα-1. This behavior clearly distinguishes neublastin from GDNF; as shown in FIG. 11, GDNF binds to GFRα-1 but not to GFRα-3.

It is clear from this data that GDNF acts on GFRα-1 and ARTN/NBN acts on GFRα-3 and that there is no cross-talk.

2/ Milbrandt at column 39, line 66 to column 40, line 1.

3/ Milbrandt at column 42, lines 6-11 (emphasis added).

4/ Rakowicz WP, Staples CS, Milbrandt J, Brunstrom JE, Johnson EM Jr., "Glial cell line-derived neurotrophic factor promotes the survival of early postnatal spinal motor neurons in the lateral and medial motor columns in slice culture;" *J Neurosci.* 2002 May 15;22(10):3953-62.

5/ *Biochemistry*. 2005 Feb 22;44(7):2545-54.

6/ See *e.g.*, Specification at Figure 11.

7/ Specification at page 55, lines 19-21.

As such, ARTN/NBN is structurally and functionally distinct from GDNF. Accordingly, this does not create a scenario where a person of ordinary skill in the art could easily substitute one element of the prior art for another. The examiner relies on the general teachings in Yan and Milbrandt that identify ARTN/NBN and GDNF generally as neurotrophic growth factors. The Office Action, however, fails to consider the distinct modes of action by which these growth factors elicit their biological effect. That ARTN/NBN and GDNF are generally known in the art as neurotrophic growth factors can not support a conclusion that the claims would have been obvious to one of ordinary skill in the art.

Furthermore, as is explained by the Federal Circuit, the motivation to combine is part of the discussion in determining the scope and content of the prior art.[8/] Thus, where all claim limitations are found in a number of references, the factfinder must determine "[w]hat the prior art teaches… and whether it motivates a combination of teachings from different references".[9/] Here, Milbrandt fails to disclose a method of using ARTN/NBN for the treatment of an eye disorder such as macular degeneration, retinitis pigmentosa, or glaucoma. Nowhere in Milbrandt is it even taught that ARTN/NBN is expressed in the retina. Thus, there is no suggestion in Milbrandt that ARTN/NBN may be used in the manner now claimed. Yan discloses the use of GDNF, which as above, is a structurally different protein and produces its biological effect through a different biological mechanism. A person of ordinary skill in the art would appreciate these differences and would not have been motivated to combine the teachings of Yan and Milbrandt to arrive at the present invention. Because of the structural and functional differences between ARTN/NBN and GDNF, a person of ordinary skill in the art would not "be able to fit the teachings of multiple patents together like pieces of a puzzle."[10/]

8/ DyStar Textilfarben GmbH & Co. Deutschland KG v. C.H. Patrick Co., 464 F.3d 1356, 1360, 80 USPQ2d 1641, 1645 (Fed. Cir. 2006); *citing* SIBIA Neurosciences, Inc. v. Cadus Pharma. Corp., 225 F.3d 1349, 1356 (Fed. Cir. 2000).

9/ *Id.* citing In re Fulton, 391 F.3d 1195, 1199-1200 (Fed. Cir. 2004).

10/ KSR, 82 USPQ2d at 1397.

In view of the above, Applicants respectfully submit that the Office Action fails to set forth a *prima facie* case of obviousness. Accordingly, Applicants request withdrawal of this rejection.

35 U.S.C. § 103(a): Yan, Milbrandt, and Hammang

Claims 80-83 and 87-93 are rejected under 35 U.S.C. § 103(a) as allegedly being unpatentable over Yan *et al.* (U.S. Patent No. 5,641,749; "Yan") in view of Milbrandt *et al.* (U.S. Patent No. 6,284,540; "Milbrandt"), as applied to claims 80-83, 87-90, and 93 above, and further in view of Hammang *et al.* (U.S. Patent No. 6,299,895; "Hammang"). Applicants respectfully request withdrawal of this rejection for the reasons provided herein.

The examiner maintained this rejection under the rationale that Milbrandt teaches that "NBN/ARTN can bind and activate GFRα1"[11/] As explained above, however, these conclusions are not factually supported by Milbrandt, nor are they supported by the general understanding in the art. As explained in the Declaration of Teit Johansen filed herewith, Milbrandt is an author of a paper, Rakowicz, that reports GDNF is the exclusive physiological ligand for GFRα-1.[12/] A subsequent study by Carmillo[13/] confirms the findings of Rakowicz. Accordingly, the teachings of Milbrandt (US 6,284,549) have been demonstrated as incorrect, or in the least, as not physiologically relevant. Indeed, the evidence of record indicates that Milbrandt has himself admitted that GDNF is the exclusive physiological ligand for GFRα-1. Applicants maintain that GDNF and ARTN/NBN are structurally distinct and that the skilled artisan cannot extrapolate the biological activity of GDNF to ARTN/NBN.

11/ Office Action at page 7, lines 3-4.

12/ Rakowicz WP, Staples CS, Milbrandt J, Brunstrom JE, Johnson EM Jr., "Glial cell line-derived neurotrophic factor promotes the survival of early postnatal spinal motor neurons in the lateral and medial motor columns in slice culture;" *J Neurosci.* 2002 May 15;22(10):3953-62.

13/ *Biochemistry*. 2005 Feb 22;44(7):2545-54.

Hammang does not cure the above noted deficiency of Milbrandt. Hammang is relied upon by the Examiner for its teaching of GDNF in the treatment of macular degeneration and retinitis pigmentosa as recited in claims 80, 91, and 92. Hammang does not teach NBN/ARTN, nor does Hammang teach or suggest the use of NBN/ARTN in the treatment of macular degeneration or retinitis pigmentosa. Because GDNF is functionally distinct from NBN/ARTN, one of ordinary skill in the art would not have be motivated to substitute GDNF for ARTN/NBN with a reasonable expectation of success. The Office Action fails to set forth a rationale as to why a person of ordinary skill in the art would expect two structurally and functionally distinct polypeptides operating through distinct receptor pathways to be obvious substitutions for one another. Rather, this rejection has been improperly maintained in view of a conclusion that is not supported by the evidence of record. Withdrawal of this rejection is respectfully requested.

§ 35 U.S.C. § 112, first ¶ - enablement

Claims 80-83 and 87-93 are rejected for allegedly failing to satisfy the enablement requirement under 35 U.S.C. § 112, first ¶. Applicants disagree with this rejection. Nonetheless, claim 80 is amended to recite an amino acid sequence that is at least 95% identical to the full length of amino acid sequence of SEQ ID NO: 12. Applicants request reconsideration of this rejection in view of the present claim amendments.

§ 35 U.S.C. § 112, first ¶ - written description

Claims 80-83 and 87-93 are rejected for allegedly failing to satisfy the written description requirement under 35 U.S.C. § 112, first ¶. Applicants disagree with this rejection. Nonetheless, claim 80 is amended to recite an amino acid sequence that is at least 95% identical to the full length of amino acid sequence of SEQ ID NO: 12. Applicants request reconsideration of this rejection in view of the present claim amendments.

CONCLUSION

An indication of allowance of all claims is respectfully solicited. Early notification of a favorable consideration is respectfully requested. In the event any issues remain, Applicant would appreciate the courtesy of a telephone call to their counsel to resolve such issues and place all claims in condition for allowance.

Respectfully submitted,

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